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A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study of the Effects of Qili Qiangxin Capsules in Patients With Chronic Heart Failure

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Objectives The purpose of this study was to assess the effects of qili qiangxin capsules in patients with chronic heart failure (CHF).

Background Qili qiangxin capsules are a traditional Chinese medicine that has been approved in China for the treatment of CHF, but the evidence supporting its efficacy remains unclear.

Methods A total of 512 patients with CHF were enrolled and randomly assigned to receive the placebo or qili qiangxin capsules in addition to their standard medications for the treatment of CHF. The primary endpoint was the reduction or percent change in the plasma N-terminal pro–B-type natriuretic peptide (NT-proBNP) level during 12 weeks of treatment.

Results At the 12-week follow-up, a significant reduction in the NT-proBNP level from baseline was observed in both groups, but the qili qiangxin capsule group demonstrated a significantly greater reduction than the placebo group ($p = 0.002$); 47.95% of patients in the qili qiangxin capsule group demonstrated reductions in NT-proBNP levels of at least 30% compared with 31.98% of patients in the placebo group ($p < 0.001$). Treatment with qili qiangxin capsules also demonstrated superior performance in comparison to the placebo with respect to New York Heart Association functional classification, left ventricular ejection fraction, 6-min walking distance, and quality of life.

Conclusions On a background of standard treatment, qili qiangxin capsules further reduced the levels of NT-proBNP. Together, our data suggest that qili qiangxin capsules could be used in combination therapy for CHF. (J Am Coll Cardiol 2013;62:1065–72) © 2013 by the American College of Cardiology Foundation

Chronic heart failure (CHF) is a public health problem worldwide and an important topic in clinical cardiology. Evidence from epidemiological studies has demonstrated that the incidence of heart failure in Chinese adults is 0.9%, 0.7%, and 1.0% for the general population, men, and women, respectively (1). According to the guidelines for CHF treatment, diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, aldosterone receptor antagonists, digitalis, and vasodilating agents should be used as standard treatments for heart failure

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Abbreviations and Acronyms

6MWD = 6-min walking distance

CCE = composite cardiac event(s)

CHF = chronic heart failure

LVEF = left ventricular ejection fraction

MLHFQ = Minnesota Living With Heart Failure Questionnaire

NT-proBNP = N-terminal pro–B-type natriuretic peptide

TCM = traditional Chinese medicine

(2–4). Despite advances in the drug treatment strategy for heart failure, the number of deaths resulting from this condition continues to rise.

From the perspective of traditional Chinese medicine (TCM), the primary cause of heart failure is heart Yang deficiency that results from Qi inadequacy and blood stasis. Some Chinese herbs have demonstrated safety and efficacy in the management of heart failure in either animal models or humans (5–8). Qili qiangxin capsules are a specific TCM extract obtained from 11 types of herbs, including astragali radix, ginseng radix et rhizoma, aconiti lateralis radix preparata, *Salvia miltiorrhiza* radix et rhizoma, semen descurainiae lepidii, alismatis rhizoma, polygonati odorati rhizoma, cinnamomi ramulus, carthami flos, periploca cortex, and citri reticulatae pericarpium. Astragali radix and aconiti lateralis radix preparata are the principal pharmacologically active components. Qili qiangxin capsules were approved by China Food and Drug Administration for the treatment of heart failure in 2004.

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The current study evaluated the effects of qili qiangxin capsules in patients with CHF. The primary endpoint was the plasma N-terminal pro–B-type natriuretic peptide (NT-proBNP) level, and the secondary endpoints consisted of composite cardiac events (CCEs), New York Heart Association (NYHA) functional classification, 6-min walking distance (6MWD), echocardiographic measures, and patient quality of life.

Methods

Design and eligibility. The primary objective of this study was to assess whether qili qiangxin capsules were superior to a placebo for CHF treatment. This study was designed as a multicenter, randomized, double-blind, placebo-controlled study based on standard therapy and parallel groups. The target enrollment was 512 patients at 23 clinical research centers in China. The enrollment criteria consisted of patients aged 18 to 75 years and clinical findings of CHF for at least 3 months prior to screening. Both men and women were included. CHF was diagnosed according to the Chinese guidelines published in 2007 for the diagnosis and management of CHF (5). The patients were clinically stable, had an NYHA functional class of II to IV, and had received optimal medical treatment with a fixed dosage for at least 2 weeks. To be included in this trial, patients had to have a documented left ventricular ejection fraction (LVEF) $\leq$40% and a serum NT-proBNP level $\geq$450 pg/ml. Patients were excluded if CHF was caused by valvular disease, congenital heart disease, pericardial disease, cardiac arrhythmia, or other noncardiogenic factors. In addition, patients were excluded if they were likely to undergo coronary artery bypass graft surgery during the following 12 weeks; had undergone or were likely to undergo cardiac resynchronization therapy; had uncorrected primary valvular disease, left ventricular outflow obstruction, myocarditis, aneurysm, uncontrolled severe arrhythmia, cardiogenic shock, unstable angina, or acute myocardial infarction; had severe primary hepatic, renal, or hematologic disease; or had a severe mental health condition or other uncontrolled systemic disease. Finally, patients were excluded if they had a serum creatinine level $>$194.5 μmol/l or serum potassium level $>$5.5 mmol/l; had alanine aminotransferase or alkaline phosphatase levels $>$1.5 times the upper normal limit; had uncontrolled blood pressure, with a systolic blood pressure $\geq$180 mm Hg or a diastolic blood pressure $\geq$110 mm Hg; were pregnant or lactating; were known or suspected to be allergic to the study drugs; had received another investigational drug within 30 days prior to randomization; or were unwilling or unable to provide written consent.

Study protocol. In this double-blind trial, patients were evaluated based on self-reported history, physical examinations, laboratory screening, and transthoracic Doppler echocardiography. Eligible patients were randomly assigned to 2 groups that received either qili qiangxin capsules or a placebo (in a 1:1 ratio; the treatments were provided as capsules that were identical in size and shape) in addition to their usual care or medications prescribed for CHF by the attending physicians. The study medication was labeled with sequential randomization numbers, and each patient was assigned the lowest number available at each site at the randomization visit. The dosage used in this study was 4 capsules of qili qiangxin or placebo 3 times daily. Patients attended follow-up appointments at the fourth, 8th, and 12th weeks of treatment. At each visit, patients were asked about the occurrence of any clinical event or adverse effect; in addition, symptoms were reviewed, vital signs were measured, and the dose of the study drug was recorded. At each visit, the participants were required to complete the Minnesota Living With Heart Failure Questionnaire (MLHFQ), one of the most widely used questionnaires to assess heart failure. Echocardiography and the 6MWD test were performed at baseline and at the last visit. LVEF was estimated using the biplane Simpson method. The entire study period lasted 12 weeks.

The study protocol was reviewed and approved by the appropriate independent ethics committees. All participants provided written informed consent, and the study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The trial was registered at ChiCTR-TRC-11001478.

Laboratory tests. Routine laboratory tests (complete blood count, urinalysis, and serum chemistry profile) were performed in the local laboratories of the participating institutions. The

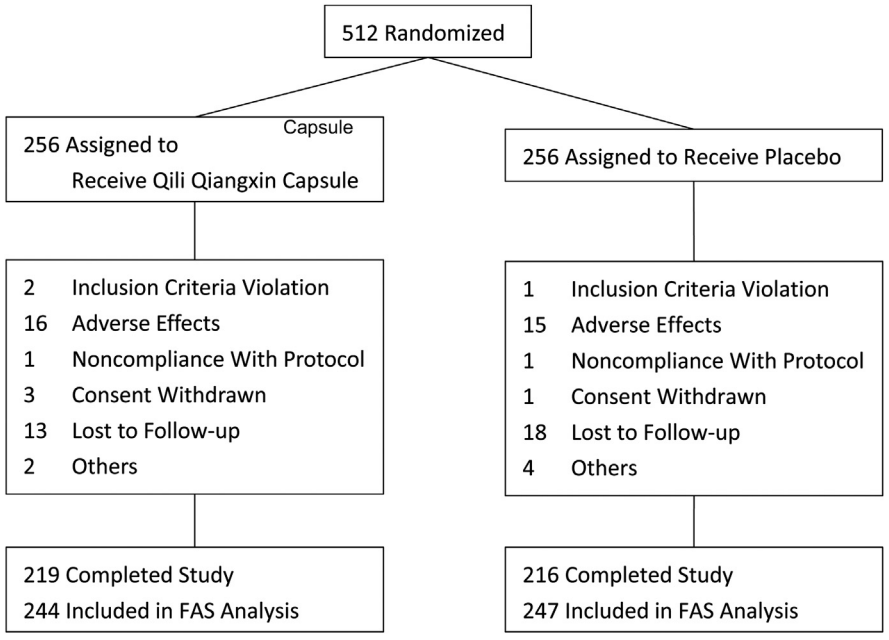


Figure 1 Flow Diagram Illustrating the Number of Patients in Each Group Throughout the Study

FAS = full analysis set.

estimated glomerular filtration rate was calculated according to the modified estimated glomerular filtration rate equation for Chinese patients (9). Plasma NT-proBNP levels were measured in the Department of Laboratory Medicine, First Affiliated Hospital of Nanjing Medical University, Nanjing, China, using dedicated kit-based NT-proBNP assays (Roche Diagnostics, Basel, Switzerland).

Endpoints. The primary endpoint was either the percent reduction in plasma NT-proBNP level or the proportion of patients in the qili qiangxin capsule group relative to the placebo group demonstrating a decrease in NT-proBNP level of at least 30%. The secondary endpoints included CCEs, NYHA classification, 6MWD test results, echocardiographic measures, and quality of life. CCEs were defined as death, cardiac arrest with resuscitation, re-admission for heart failure, worsening heart failure with an intravenous pharmacological agent for more than 4 h, stroke, or cases in which the patient ceased active treatments because of worsening heart failure. The assessments of safety and tolerability were based on spontaneous reports of adverse events, vital signs, and laboratory measurements.

Sample size calculation. The sample size was calculated based on the expected reduction in plasma NT-proBNP levels from pre- to post-treatment. A previous study suggested that the prognosis of patients whose NT-proBNP levels decreased by at least 30% from baseline with therapy was significantly better than for patients with no significant change or an increase in NT-proBNP levels (10). Therefore, assuming a 38% reduction in plasma NT-proBNP level following-treatment with qili qiangxin capsules (i.e., 30% greater reduction than basic therapy), and given a type I error rate of alpha = 0.05, a power of 80% (type II error rate of beta = 0.2), and the normal SD of 30%, the sample size for 1 arm needed to be 175, resulting in $n = 2 \times 175 = 350$ patients. Moreover, considering a dropout rate of approximately 20% among randomized patients, a total of 420 patients (210 per treatment group) needed to be randomized to achieve the required number of patients for the efficacy analysis.

The sample size was also calculated based on the expected proportion of patients demonstrating an NT-proBNP level decrease of at least 30%. According to previous clinical results, we assumed the proportion of patients demonstrating a decrease in NT-proBNP level of at least 30% in the placebo group would be 40%, 12% lower than the tested group. Therefore, given a type I error rate of alpha = 0.05, a power of 80% (type II error rate of beta = 0.2), the sample size for 1 arm needed to be 213, resulting in $n = 2 \times 213 = 426$ patients. Moreover, considering a dropout rate of approximately 20% for randomized patients, a total of 512 patients (256 per treatment group) needed to be randomized to achieve the required number of patients for the efficacy analysis.

Under these 2 assumptions, we recruited 512 patients to the study, who were subsequently allocated at a 1:1 ratio to the qili qiangxin capsule group or the placebo group.

Statistical analysis. All statistical analyses were performed with SAS software, version 9.2 (SAS Institute, Cary, North Carolina). Data from all patients who underwent randomization were analyzed according to the full analysis set principle. Continuous variables are presented as the mean ± SD. The comparability of the characteristics

Table 1 Baseline Characteristics of Patients Receiving Qili Qiangxin Capsules or Placebo

Characteristic	Qili Qiangxin Capsules (n = 244)	Placebo (n = 247)	All (N = 491)
Course of disease, months	77.25 ± 10.94	77.14 ± 11.27	77.20 ± 11.10
Demographics			
Age, yrs	56.98 ± 11.59	57.53 ± 11.05	57.25 ± 11.31
Male	74.59	76.11	75.36
Race			
Han	98.77	98.79	98.78
Other	1.23	1.21	1.22
Measurements			
Weight, kg	68.63 ± 12.32	68.80 ± 13.05	68.72 ± 12.68
Height, cm	167.28 ± 7.71	167.13 ± 7.06	167.20 ± 7.39
Systolic BP, mm Hg	120.44 ± 16.43	120.42 ± 17.18	120.43 ± 16.80
Diastolic BP, mm Hg	77.25 ± 10.94	77.14 ± 11.27	77.20 ± 11.10
Heart rate, beats/min	78.41 ± 13.69	77.84 ± 13.36	78.12 ± 13.51
Etiology of CHF			
Cardiomyopathy	58.61	55.06	56.82
Ischemic heart disease	31.56	33.60	32.59
Hypertension	16.80	22.67	19.76
Other*	0.82	3.64	2.24
Medical history			
Atrial fibrillation	14.34	16.60	15.48
Diabetes mellitus	13.93	19.43	16.7
Medication			
ACE inhibitors	169 (69.26)	157 (63.56)	326 (66.40)
Angiotensin receptor blockers	51 (20.90)	48 (19.43)	99 (20.16)
Beta-blockers	191 (78.28)	196 (79.35)	387 (78.82)
Aldosterone antagonists	190 (77.87)	201 (81.38)	391 (79.63)
Diuretics	220 (90.16)	222 (89.88)	442 (90.02)
Digoxin	127 (52.05)	136 (55.06)	263 (53.56)
NYHA functional class			
I	0	0	0
II	52.46	53.44	52.95
III	41.80	41.70	41.75
IV	5.74	4.86	5.3
Echocardiography measurements			
LVEF, %	31.85 ± 6.41	31.86 ± 6.46	31.85 ± 6.43
LVED, mm	66.54 ± 10.13	66.63 ± 10.67	66.59 ± 10.39
Laboratory measurements			
Sodium, mmol/l	139.86 ± 3.84	139.78 ± 3.78	139.82 ± 3.80
Potassium, mmol/l	4.30 ± 0.57	4.33 ± 0.61	4.31 ± 0.59
Creatinine, μmol/l	84.40 ± 25.01	89.85 ± 40.21	87.19 ± 33.73
eGFR, ml/min/1.73 m^2†	97.22 ± 57.39	91.31 ± 34.00	94.20 ± 46.95
Hemoglobin, g/l	140.95 ± 18.39	139.70 ± 18.76	140.32 ± 18.57
Plasma NT-ProBNP, pg/ml	3,204.36 ± 4,260.22	3,224.64 ± 4,985.90	3,214.56 ± 4,634.77
Median (Q1, Q3)	1,818.00 (910.45, 3,613.50)	1,815.00 (973.60, 3,172.00)	1,815.00 (962.30, 3,327.00)
6MWD, m	376.57 ± 98.39	350.85 ± 82.43	363.64 ± 91.40
MLHFQ	34.91 ± 17.67	35.48 ± 17.22	35.20 ± 17.43

Values are mean ± SD , %, n (%), or median (Q1, Q3). *Statistically significant at $p < 0.05$ (qili qiangxin capsule group vs. placebo group). †Estimated glomerular filtration rate (eGFR; ml/min/1.73 m^2) = 175 × creatinine$^{-1.234}$ × age$^{-0.179}$ × 0.79 (if female); creatinine levels in μmol/l can be converted to mg/dl by dividing them by 88.4.

6MWD = 6-min walking distance; ACE = angiotensin-converting enzyme; BP = blood pressure; CHF = chronic heart failure; LVED = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MLHFQ = Minnesota Living With Heart Failure Questionnaire; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association.

between the 2 study groups was assessed using a 2-sample Student *t* test for continuous variables and the chi-square test or Wilcoxon test, when appropriate, for categorical variables. The Wilcoxon paired signed-rank test was used for within-group comparisons. Values of < 0.05 were considered statistically significant, and all tests were 2 tailed.

Results

From September 2011 to July 2012, 512 patients underwent randomization at 23 sites in China; the flow diagram of patients through the study is presented in Figure 1. The baseline characteristics of the study groups

Table 2 Change in Plasma NT-ProBNP Levels From Baseline to After 12 Weeks of Follow-Up

	Qili Qiangxin Capsules (n = 244)	Placebo (n = 247)	p Value
Difference in NT-proBNP, pg/ml	240.15 (−23.15, 1,113.85)	0.00 (−286.00, 800.00)	0.002
Median percent reduction in NT-proBNP, %	24.70 (−1.55, 63.70)	0.00 (−18.08, 43.79)	<0.001
Proportion of patients with reduction in NT-proBNP of ≥30%, %	47.95	31.98	<0.001

Values are the median (Q1, Q3) or the % of patients. Difference in NT-proBNP = baseline level − 12-week level. Percent reduction in NT-proBNP = (baseline level − 12-week level)/baseline level × 100%.
Abbreviation as in Table 1.

are shown in Table 1. The mean age of the total population was 57.25 years, and 75.36% were male. The average course of CHF was 77.2 months. The CHF etiologies included cardiomyopathy (56.82%), ischemic heart disease (32.59%), hypertension (19.76%), and other conditions (2.24%). The distributions of the demographic and clinical characteristics between the qili qiangxin capsule group and the placebo group were well balanced and homogeneous.

Change in plasma NT-proBNP level. A favorable effect of qili qiangxin capsules was observed on the plasma NT-proBNP level (Table 2). After 12 weeks of treatment, both groups showed a significant decrease in NT-proBNP levels from baseline, but treatment with qili qiangxin capsules led to a significantly greater reduction than did the placebo (240.15 pg/ml [Q1, Q3: 23.15, 1,113.85]) vs. 0.00 pg/ml [Q1, Q3: 286.00, 800.00]; p = 0.002). The mean percent reductions in NT-proBNP level for the qili qiangxin capsule and placebo groups were 24.70% (Q1, Q3: 1.55%, 63.70%) and 0.00% (Q1, Q3: 18.08%, 43.79%) (p < 0.001), respectively. A total of 47.95% of the patients in the qili qiangxin capsule group had reductions in NT-proBNP levels of at least 30%, compared with 31.98% of patients in the placebo group (p < 0.001).

CCEs. Table 3 presents the rates of CCEs for both groups. Overall, 4.51% and 10.93% of patients in the qili qiangxin and placebo groups experienced CCEs, respectively (p = 0.008).

NYHA functional classification. The NYHA class was determined at each visit. As shown in Figure 2, there was no difference between the 2 groups at baseline. The frequency of NYHA I patients gradually increased, whereas the frequency of NYHA III to IV patients gradually decreased after treatment with either qili qiangxin capsules or placebo accompanied by background treatment. In this analysis, qili qiangxin capsule treatment resulted in superior improvements at the 8- and 12-week visits compared with the placebo (p = 0.005 and p < 0.001, respectively).

Echocardiography measurements and 6MWD. At baseline and at the 12-week visit, echocardiography and the 6MWD test were performed. As shown in Table 1, the parameters of the echocardiography measurements and the 6MWD did not differ between the 2 groups at baseline, and great improvement was observed after treatment with either qili qiangxin capsules or placebo accompanied by the background therapy at the 12-week visit (p < 0.001 for all) (Fig. 3). Compared with patients randomized to the placebo treatment group, patients receiving qili qiangxin capsule treatment exhibited greater improvements in LVEF and 6MWD (p = 0.001; 95% CI: 0.03 to 0.15 and p = 0.006; 95% CI: −0.03 to 0.13, respectively) but not in left ventricular end-diastolic diameter (p = 0.519; 95% CI: −0.04 to 0.01).

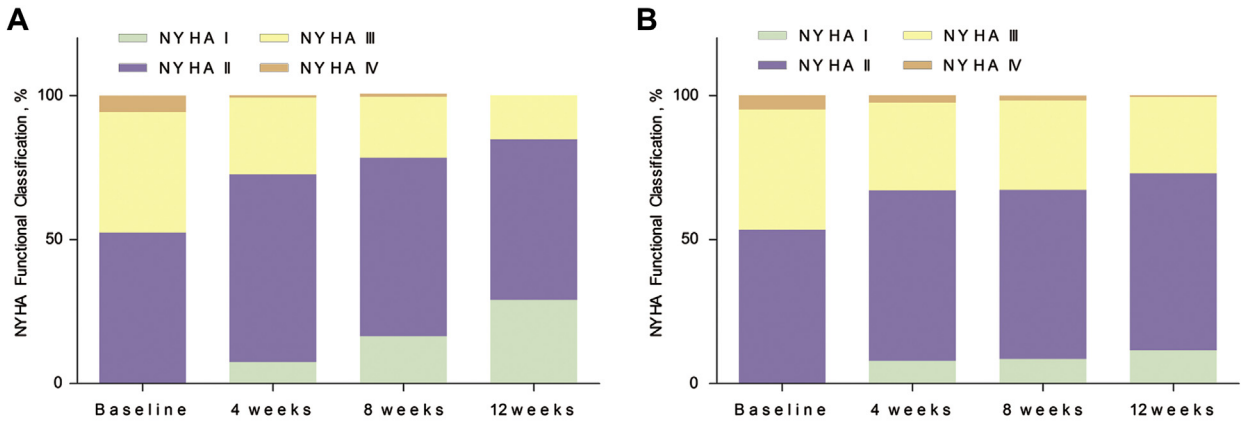
Quality of life assessment using the MLHFQ. The MLHFQ was completed at each visit, and the 2 groups demonstrated similar mean MLHFQ scores at baseline (Table 1). Overall, there was a gradual improvement in the mean MLHFQ score during the entire treatment period, and significant effects of qili qiangxin capsule treatment compared with placebo were observed at the 4-, 8-, and 12-week visits (p < 0.001 for all), as shown in Figure 4.

Adverse events. A total of 250 patients in each group were included in the safety set analyses (Table 4). The total

Table 3 CCEs of Patients Receiving Qili Qiangxin Capsule Therapy or Placebo

CCEs*	Qili Qiangxin Capsules (n = 244) n = 11 (4.51%)	Placebo (n = 247) n = 27 (10.93%)
Death	4 (1.64)	7 (2.83)
Cardiac arrest with resuscitation	0	1 (0.40)
Re-admission for HF	8 (3.28)	16 (6.48)
Worsening HF with an intravenous pharmacological agent	0	2 (0.81)
Stroke	1 (0.41)	1 (0.40)
Patient abandonment for worsening HF	0	1 (0.40)

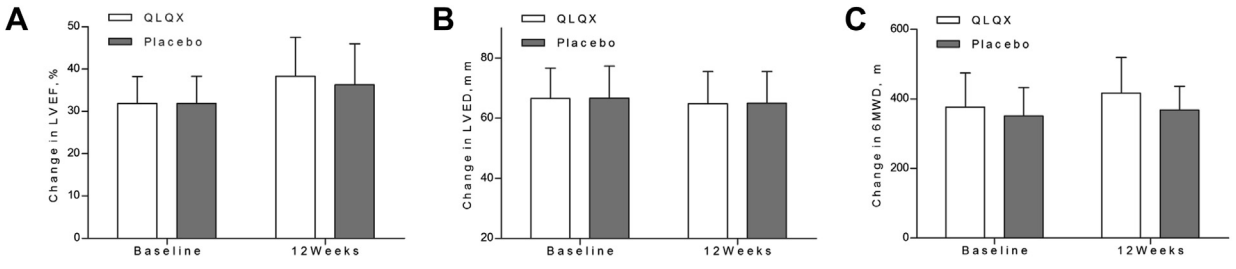
Values are n (%). Some patients reported more than 1 event. *Statistically significant at p = 0.008.
CCE = composite cardiac event(s); HF = heart failure.



	Qili Qiangxin Capsule				Placebo				p value
	NYHA I	NYHA II	NYHA III	NYHA IV	NYHA I	NYHA II	NYHA III	NYHA IV	
Baseline	0%	52.46%	41.80%	5.74%	0%	53.44%	41.70%	4.86%	0.904
4 weeks	7.47%	65.15%	26.56%	0.83%	7.82%	59.26%	30.45%	2.47%	0.350
8 weeks	16.45%	61.90%	21.21%	1.00%	8.51%	58.72%	31.06%	1.70%	0.005
12 weeks	29.03%	55.76%	15.21%	0%	11.63%	61.40%	26.51%	0.47%	<0.001

Figure 2 NYHA Functional Classification Results

(A) Qili qiangxin capsule group. **(B)** Placebo group. NYHA = New York Heart Association.



	Qili Qiangxin Capsule			Placebo			P value
	Baseline	12 Weeks	P value	Baseline	12 Weeks	P value	(95% CI)
Echocardiography							
LVEF, %	31.85 ± 6.41	38.31 ± 9.21	<0.001	31.86 ± 6.46	36.28 ± 9.72	<0.001	
Mean change rate of LVEF	0.23 ± 0.33			0.14 ± 0.28			0.001 (0.03-0.15)
LVED, mm	66.54 ± 10.13	64.75 ± 10.73	<0.001	66.63 ± 10.67	65.02 ± 10.50	<0.001	
Mean change rate of LVED	-0.03 ± 0.08			-0.01 ± 0.16			0.519 (-0.04,0.01)
6MWD, m	376.57 ± 98.39	416.52 ± 102.74	<0.001	350.85 ± 82.43	368.08 ± 67.95	<0.001	
Mean change rate of 6MWD	0.14 ± 0.22			0.09 ± 0.29			0.006 (-0.03,0.13)

Figure 3 Echocardiography Measurements and 6MWD Changes From Baseline to After 12 Weeks of Treatment

Values are expressed as mean ± SD. The mean rate of change ([12-week level − baseline level]/baseline level) of **(A)** left ventricular ejection fraction (LVEF), **(B)** left ventricular end-diastolic diameter (LVED), and **(C)** 6-min walking distance (6MWD) test.

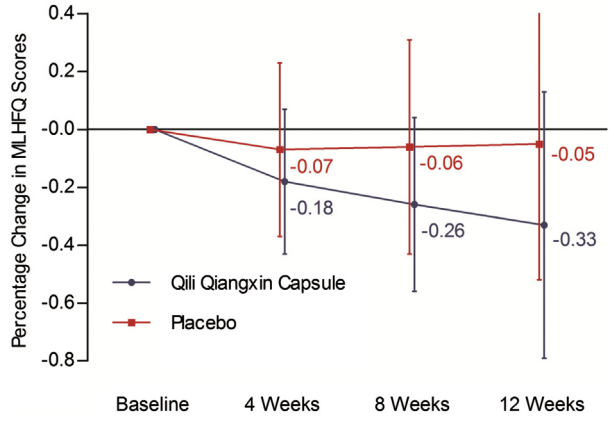


Figure 4 **Percent Change in the MLHFQ Scores From Baseline Through 12 Weeks of Follow-Up**

MLHFQ = Minnesota Living With Heart Failure Questionnaire.

number of adverse events was 66 in the qili qiangxin capsule group versus 98 in the placebo group (p = 0.122); for serious adverse events, the total number was 12 in the qili qiangxin capsule group versus 22 in the placebo group (p = 0.103). Some patients reported more than 1 event. There was no report of any serious adverse events related to the study drugs. The analysis of drug-induced adverse events and withdrawal revealed no differences between the study groups.

Discussion

CHF is clinically associated with high mortality, high morbidity, decrease in quality of life, and substantial burden on health care systems. The purpose of diagnosing and treating CHF is to reduce patient mortality and morbidity (3). The prognosis for patients with CHF has improved in the past 2 decades, largely because of the use of neurohormonal antagonists such as angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone antagonists, but the prognosis remains poor. It is therefore crucial to develop novel therapeutic approaches for the treatment of CHF.

Qili qiangxin is a widely used TCM for the treatment of CHF, and its efficacy against cardiac hypertrophy and remodeling has been demonstrated in several studies. Xiao et al. (11) investigated the effects of qili qiangxin powder on cardiac function in rats with myocardial infarction and found that qili qiangxin treatment significantly improved cardiac function and histopathologic changes, with a down-regulated ratio of tumor necrosis factor alpha/interleukin 10. One possible mechanism underlying the beneficial effects of qili qiangxin may involve the regulation of the balance between proinflammatory and anti-inflammatory cytokines in cardiomyocytes (11). In addition, Liu et al. (12) found that the original superfine qili qiangxin powder improved both systolic and diastolic cardiac function in spontaneously hypertensive rats by down-regulating the cardiac chymase signaling pathway and chymase-mediated angiotensin II production. Zou et al. (13) examined the effects of qili qiangxin powder on the development of cardiac hypertrophy in mice with underlying transverse aorta constriction and found that qili qiangxin inhibited myocardial inflammation and cardiomyocyte death and promoted cardiomyocyte proliferation, leading to improved cardiac remodeling and cardiac function. The mechanisms of qili qiangxin may involve inhibition of the angiotensin II type 1 receptor and activation of ErbB receptors (13). (A mini-review is provided in the Online Appendix).

NT-proBNP, a biologically inactive fragment of BNP, is released by the heart in response to myocardial tension and increased intravascular volume. Elevated levels of circulating NT-proBNP assist in the diagnosis of heart failure and are associated with increased mortality and morbidity in patients with heart failure (14–16). Moreover, NT-proBNP can be accurately measured in the laboratory, and the magnitude

Table 4 **Summary of Adverse Events**

	Qili Qiangxin Capsules (n = 250)		Placebo (n = 250)		
	n (Case)	%	n (Case)	%	p Value
AEs	55 (66)	22.00	71 (98)	28.40	0.122
AEs related to study drugs	19 (20)	7.60	23 (23)	9.20	0.629
SAEs	12 (12)	4.80	21 (22)	8.40	0.103
Death*	4	2.00	9	3.60	
Hospitalization					
Arterial occlusive diseases	0	0	1	0.40	
Worsening heart failure	4	1.6	7	2.8	
Stroke	1	0.40	1	0.40	
Lumbar fracture	1	0.40	0	0	
Unknown reason	2	0.80	3	1.20	
Withdrew due to study drugs	15 (14)	5.60	17 (17)	6.80	0.711

The analysis included all patients who received at least 1 dose of the study medication. Some patients reported more than 1 event. *Two dead patients in the placebo group were not included in the full analysis set analysis.

AE = adverse event(s); SAE = serious adverse event(s).

of change can be used as an endpoint for clinical trials focused on heart failure. The results of our study suggest that qili qiangxin capsules can markedly reduce NT-proBNP levels, which suggests that patients may receive an improved prognosis with long-term treatment. However, a large, randomized, controlled study using all-cause mortality as the endpoint is needed to test this hypothesis.

The CCE results indicated favorable effects of qili qiangxin capsules, and fewer deaths and re-admissions for heart failure were observed in the qili qiangxin capsule group compared with the placebo group; however, these differences were not significant. Our results also showed that qili qiangxin capsules improved exercise tolerance and patient quality of life and resulted in improvements in both the NYHA functional class and echocardiography measurements.

Conclusions

On a background of standard treatment, qili qiangxin capsules further reduced the levels of NT-proBNP. Together, our data suggest that qili qiangxin capsules could be used in combination therapy for CHF.

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Key Words: chronic heart failure ■ qili qiangxin capsules ■ randomized controlled trial.

APPENDIX

For a supplemental mini-review of qili qiangxin capsules and a list of sites and staff that participated in this study, please see the online version of this article.